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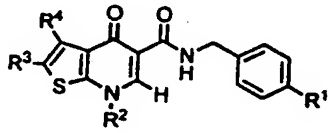
(54) Title: 4–OXO–4,7–DIHYDRO–THIENO[2,3–b]PYRIDINE–5–CARBOXAMIDES AS ANTIVIRAL AGENTS

(57) Abstract

The invention provides a compound of formula (I), wherein R^1, R^2, R^3, and R^4 have any of the values defined in the specification, or a pharmaceutically acceptable salt thereof, as well as processes and intermediates useful for preparing such compounds or salts, and methods of preventing or treating a herpesvirus infection using such compounds or salts.



(I)

4-OXO-4,7-DIHYDRO-THIENO[2,3-b]PYRIDINE-5-CARBOXAMIDES AS ANTIVIRAL AGENTS

FIELD OF THE INVENTION

The present invention provides 4-oxo-4,7-dihydro-thieno[2,3-b]pyridine-5-carboxamide derivatives, more specifically, 5-benzylaminocarbonyl-4-oxo-4,7-dihydro-thieno[2,3-b]pyridine derivatives of formula (I), which are useful as antiviral agents (e.g. as agents against viruses of the herpes family).

BACKGROUND OF THE INVENTION

The herpesviruses comprise a large family of double stranded DNA viruses. They are also a source of the most common viral illnesses in man. Eight of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans.

HSV-1 and HSV-2 cause herpetic lesions on the lips and genitals, respectively. They also occasionally cause infections of the eye and encephalitis. HCMV causes birth defects in infants and a variety of diseases in immunocompromised patients such as retinitis, pneumonia, and gastrointestinal disease. VZV is the causative agent of chicken pox and shingles. EBV causes infectious mononucleosis. It can also cause lymphomas in immunocompromised patients and has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkins disease. HHV-6 is the causative agent of roseola and may be associated with multiple sclerosis and chronic fatigue syndrome. HHV-7 disease association is unclear, but it may be involved in some cases of roseola. HHV-8 has been associated with Karposi's sarcoma, body cavity based lymphomas, and multiple myeloma.

INFORMATION DISCLOSURE

JP 8301849 discloses an array of compounds that may generically include compounds of formula I wherein R^1 is halo, and R^2 is hydrogen. The compounds are reported to be tachykinin inhibitors. No antiviral activity is reported for the compounds.

WO 97/40846 discloses a pharmaceutical comprising an LH releasing hormone agonist and an LH releasing hormone antagonist. The disclosed LH releasing hormone

(c) CN,

(d) NO_2, or

(e) F;

R^2 is

(a) H,

(b) R^5,

(c) NR^7R^8,

(d) SO_2R^9, or

(e) OR^9;

R^3 is

(a) H,

(b) halo,

(c) aryl,

(d) $S(O)_mR^6$,

(e) $(C=O)R^6$,

(f) $(C=O)OR^9$,

(g) cyano,

(h) het, wherein said het is bound via a carbon atom,

(i) OR^{10},

(j) Ohet,

(k) NR^7R^8

(l) SR^{10},

(m) Shet,

(n) $NHCOR^{12}$,

(o) $NHSO_2R^{12}$, or

(p) C_{1-7}alkyl which may be partially unsaturated and optionally substituted by one or more substituents of the group R^{11}, OR^{13}, SR^{10}, SR^{13}, NR^7R^8, halo, $(C=O)C_{1-7}$alkyl, or SO_mR^9;

R^4 is

(a) H,

(b) halo,

(c) C_{1-4}alkyl, or

R^{10} is

(a) H, or

(b) C_{1-7}alkyl optionally substituted by OH;

R^{11} is

(a) OR^{10},

(b) Ohet,

(c) Oaryl,

(d) CO_2R^{10},

(e) het,

(f) aryl, or

(g) CN;

R^{12} is

(a) H,

(b) het,

(c) aryl,

(d) C_{3-8}cycloalkyl, or

(e) C_{1-7}alkyl optionally substituted by NR^7R^8 or R^{11};

R^{13} is

(a) $(P{=}O)(OR^{14})_2$,

(b) $CO(CH_2)_nCON(CH_3)\text{-}(CH_2)_nSO_3^-M^+$,

(c) an amino acid,

(d) C(=O)aryl, or

(e) $C(=O)C_{1-7}$alkyl optionally substituted by NR^7R^8, aryl, het, CO_2H, or $O(CH_2)_nCO_2R^{14}$);

R^{14} is

(a) H, or

(b) C_{1-7}alkyl;

each i is independently 2, 3, or 4;

each n is independently 1, 2, 3, 4 or 5;

each m is independently 0, 1, or 2;

M is sodium, potassium, or lithium;

be partially unsaturated, the alkyl chain may comprise one or more (e.g. 1, 2, 3, or 4) double or triple bonds in the chain.

Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Het is a four- (4), five- (5), six- (6), or seven- (7) membered saturated or unsaturated heterocyclic ring having 1, 2, 3, or 4 heteroatoms selected from the group consisting of oxy, thio, sulfinyl, sulfonyl, and nitrogen, which is optionally fused to a benzene ring, or any bicyclic heterocycle group. Het includes "heteroaryl," which encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and 1, 2, 3, or 4 heteroatoms each selected from the group consisting of non-peroxide oxy, thio, and N(X) wherein X is absent or is H, O, C_{1-4}alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

When R^4 together with R^3 form a carbocyclic, R^4 and R^3 together can be a 3, 4, 5, or 6 membered saturated or unsaturated carbon chain.

"Amino acid," includes a residue of natural amino acid (e.g. Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well as unnatural amino acids (e.g. phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline, α-methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). An amino acid can conveniently be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus, or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine. In particular, an amino acid can conveniently be linked to the remainder of a compound of formula I through the carboxy terminus.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses

When C_{1-7}alkyl is partially unsaturated , it can specifically be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 5-hexene-1-ynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, or 5-hexynyl.

A specific value for Het is a five- (5), six- (6), or seven- (7) membered saturated or unsaturated ring containing 1, 2, 3, or 4 heteroatoms selected from the group consisting of non-peroxide oxy, thio, sulfinyl, sulfonyl, and nitrogen; as well as a radical of an ortho-fused bicyclic heterocycle of about eight to twelve ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, tetramethylene or another monocyclic het diradical thereto.

A specific value for R^1 is F, Cl, or Br.

A more specific value for R^1 is Cl.

A specific value for R^2 is H.

A specific value for R^2 is R^5, NR^7R^8, SO_2R^9, or OR^9.

A specific value for R^2 is R^5.

A more specific value for R^2 is methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, carboxymethyl, (C_{1-7} alkoxy)carbonylmethyl, 2-hydroxyethyl, 2-(2-methoxyethoxy)ethyl, 3-(2-tetrahydropyranyloxy)propyl, 2-morpholinoethyl, 2-(diethylamino)ethyl, 2-(dimethylamino)ethyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(1-methylpyrrolidin-2-yl)ethyl, 2-(diisopropylamino)ethyl, 2-pyrrolidin-1-ylethyl, 3-(dimethylamino)propyl, benzyl, 3-fluorobenzyl, 3-phenylpropyl, 2-tetrahydrofuranylmethyl, 2-pyrrolidinoethyl, 3-pyridylmethyl, or vinyl.

A more specific value for R^2 is methyl, ethyl, isopropyl, 2-hydroxyethyl, 2-(diethylamino)ethyl, or 2-(dimethylamino)ethyl.

A specific value for R^3 is H, halo, $S(O)_mR^6$, $(C=O)R^6$, $(C=O)OR^9$, cyano, or C_{1-7}alkyl which may be partially unsaturated and optionally substituted by one or more substituents of the group R^{11}, OR^{13}, SR^{10}, SR^{13}, NR^7R^8, halo, $(C=O)C_{1-7}$alkyl, and SO_mR^9.

A specific value for R^3 is C_{1-7}alkyl which may be partially unsaturated and optionally substituted by one or more substituents of the group R^{11}, OR^{13}, SR^{10}, SR^{13}, NR^7R^8, halo, $(C=O)C_{1-7}$alkyl, and SO_mR^9.

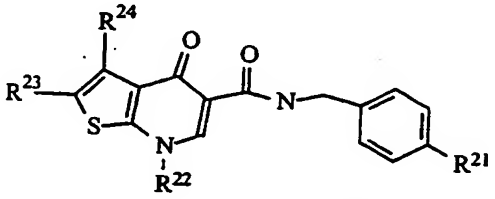
(e) CN.

A specific value for R^5 is C_{1-7}alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of NR^7R^8, R^{11}, SO_mR^9, and OC_{2-4}alkyl, which may be further substituted by het, OR^{10}, or NR^7R^8.

A specific value for R^5 is C_{1-7}alkyl, which may be partially unsaturated and is optionally substituted by one or more aryl or het.

A more specific value for R^5 is C_{1-7}alkyl.

The invention also specifically provides a compound of formula III:



(III)

or a pharmaceutically acceptable salt thereof wherein,

R^{21} is Cl, Br, CN, or NO_2;

R^{22} is H, $-(CH_2CH_2O)_nH$, $-(CH_2CH_2O)_nCH_3$, SO_2R^{35} or COR^{35}, C_{1-7}alkyl which may be partially unsaturated and optionally substituted by R^{36}, C_{2-7}alkyl which may be partially unsaturated and optionally substituted by R^{33}, or C_{3-8}cycloalkyl which may be partially unsaturated and optionally substituted by R^{36}, R^{33} or R^{34};

each R^{23} and R^{24} is independently H, halo, aryl, $S(O)_mR^{30}$, COR^{30}, cyano, het, CF_3, OR^{29}, OR^{31}, SR^{29}, SR^{31}; $NR^{25}R^{26}$, $CH(OR^{29})R^{27}$, CO_2R^{29}, $CH(CO_2R^{29})_2$, $NHCOR^{27}$, or $NHS(O)_2R^{27}$ or C_{1-7}alkyl which may be partially unsaturated and optionally substituted by R^{28};

each R^{25} and R^{26} is independently H or C_{1-7}alkyl;

R^{27} is C_{1-7}alkyl optionally substituted by R^{36} or C_{2-7}alkyl optionally substituted by R^{33};

R^{28} is cyano, halo, CF_3, aryl, het, $C(=O)C_{1-7}$ alkyl, CO_2C_{1-7}alkyl, OR^{29}, OR^{31}, OR^{32}, SR^{29}, SR^{31}, SR^{32}, $NR^{25}R^{26}$, $CH(OR^{29})R^{27}$, CO_2R^{29} or $CH(CO_2R^{29})_2$;

R^{29} is H or C_{1-7}alkyl;

Another specific value for R^{22} is C_{1-7} alkyl which may be substituted by R^{36}.

Another specific value for R^{22} is C_{2-7} alkyl which is partially unsaturated and is substituted by R^{33}.

A specific value for each R^{23} is independently H, halo, aryl, $S(O)_mR^{30}$, COR^{30}, cyano, het, CF_3, OR^{29}, OR^{31}, SR^{29}, SR^{31}, $NR^{25}R^{26}$, $CH(OR^{29})R^{27}$, CO_2R^{29}, $CH(COOR^{29})_2$, $NHCOR^{27}$, or $NHS(O)_2R^{27}$ or C_{1-7}alkyl which may be partially unsaturated and optionally substituted by R^{28};

Another specific value for each R^{23} is independently halo, $S(O)_mR^{30}$, COR^{30}, cyano, het, or C_{1-7}alkyl which may be partially unsaturated and optionally substituted by R^{28} with the proviso that at least one of R^{23} and R^{24} is hydrogen.

Another specific value for each R^{23} is independently C_{1-7}alkyl optionally substituted by R^{28} with the proviso that at least one of R^{23} and R^{24} is hydrogen.

Another specific value for each R^{23} is independently partially unsaturated C_{1-7}alkyl and optionally substituted by R^{28} with the proviso that at least one of R^{23} and R^{24} is hydrogen.

Another specific value for each R^{23} is independently (*Z* or *E*) $-CH=CH(CH_2)_nR^{28}$ or $-C\equiv C(CH_2)_nR^{28}$ with the proviso that at least one of R^{23} and R^{24} is hydrogen.

A more specific value for R^{22} is methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, carboxymethyl, (C_{1-7} alkoxy)carbonylmethyl, 2-hydroxyethyl, 2-(2-methoxyethoxy)ethyl, 3-(2-tetrahydropyranyloxy)propyl, 2-morpholinoethyl, 2-(diethylamino)ethyl, 2-(dimethylamino)ethyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(1-methylpyrrolidin-2-yl)ethyl, 2-(diisopropylamino)ethyl, 2-pyrrolidin-1-ylethyl, 3-(dimethylamino)propyl, or vinyl.

Another more specific value for R^{22} is methyl, ethyl, isopropyl, 2-hydroxyethyl, 2-(diethylamino)ethyl, or 2-(dimethylamino)ethyl.

Another more specific value R^{22} is methyl, or 2-(dimethylamino)ethyl.

Another more specific value for R^{23} is independently 3-hydroxy-1-propynyl, or 3-hydroxypropyl when R^{24} is hydrogen.

A specific compound of formula I is a compound wherein R^{21} is Cl; R^{22} is $-(CH_2CH_2O)_nH$, $-(CH_2CH_2O)_nCH_3$, SO_2R^{35}, COR^{35}, C_{1-7}alkyl which may be partially unsaturated and optionally substituted by R^{36}, C_{2-7}alkyl which may be partially unsaturated and is substituted by R^{33}, or C_{3-8}cycloalkyl which may be partially unsaturated and

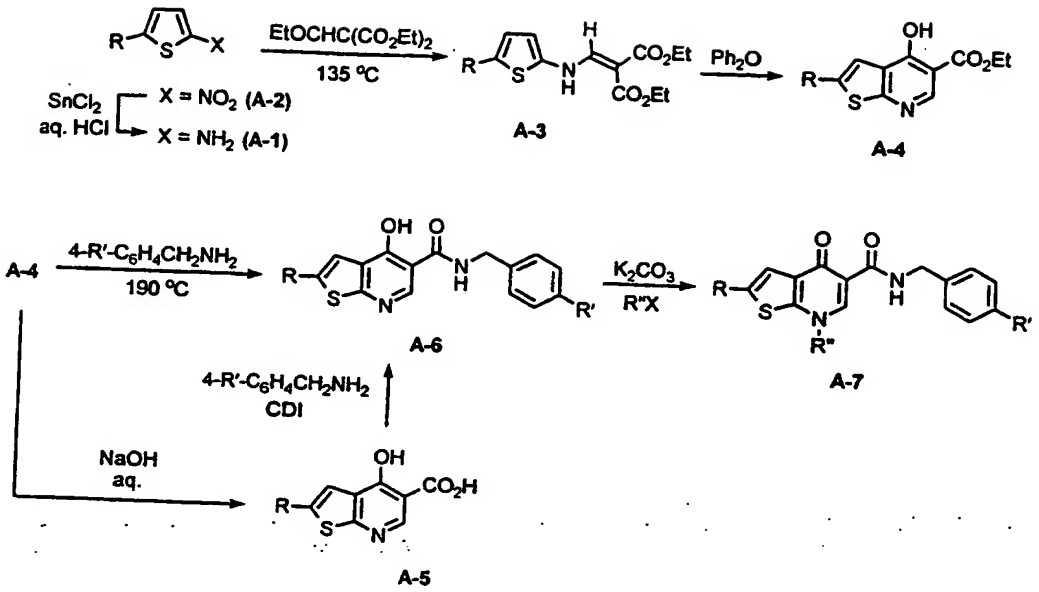


Chart B.

Compound B-1 (5-nitro-2-thiophenesulfonyl chloride) is treated with an amine to yield nitro compounds of the formula B-2. Compounds of the formula B-2 are transformed as in Chart A to yield amides analogous to A-6 and A-7.

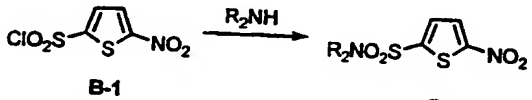


Chart C.

Compounds of the formula C-1 where R is H or alkyl are halogenated to yield compounds of the formula C-2. Compounds of the formula C-2 are transformed as in Chart A to yield amides analogous to A-6 and A-7.

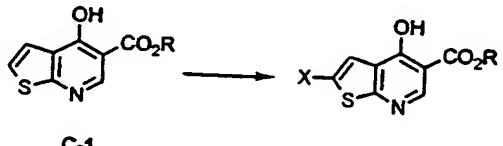
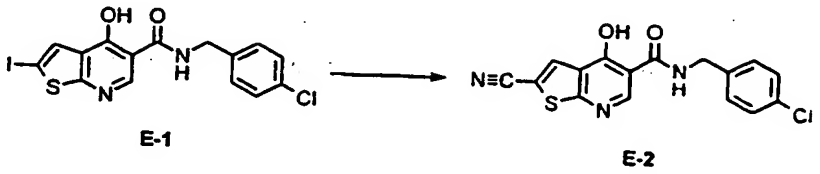


Chart E.

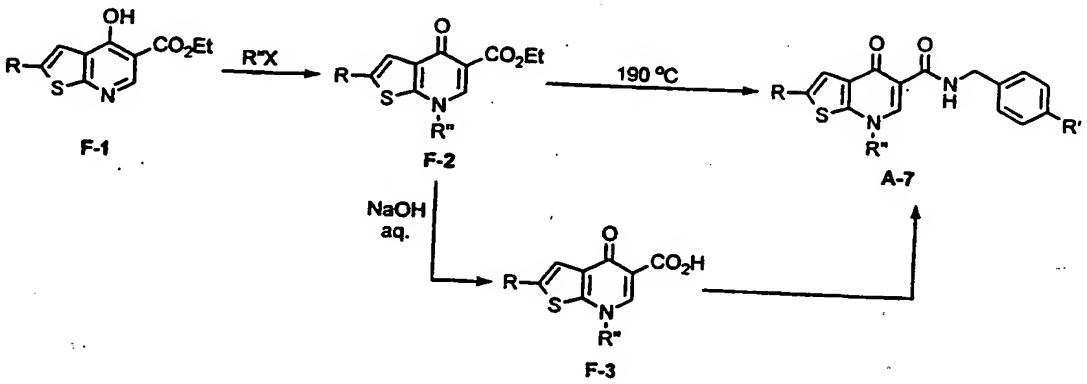
Compound E-1 is treated with copper (I) cyanide to yield the cyano compound E-2.



E-1 E-2

Chart F.

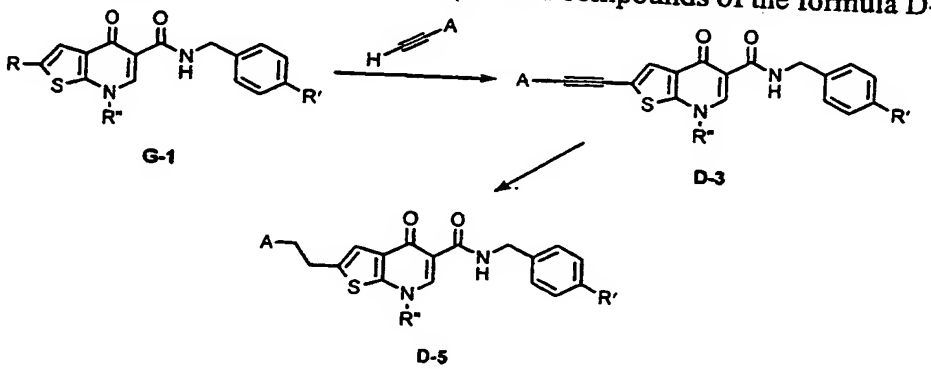
Compounds of the formula F-1 are treated with an optionally substituted alkyl halide in the presence of potassium carbonate to yield *N*-alkylated esters of the formula F-2. The esters are converted to amides of the formula A-7 via direct aminolysis with a substituted benzylamine or via hydrolysis to acids of the formula F-3 followed by treatment with carbonyldiimidazole and the amine.



F-1 F-2 A-7 F-3

Chart G.

Palladium and copper mediated coupling of G-1 (where R = Br or I) with an alkyne leads to compounds of the formula D-3. Compounds D-3 are hydrogenated using palladium on carbon as the catalyst to yield saturated compounds of the formula D-5.



G-1 D-3 D-5

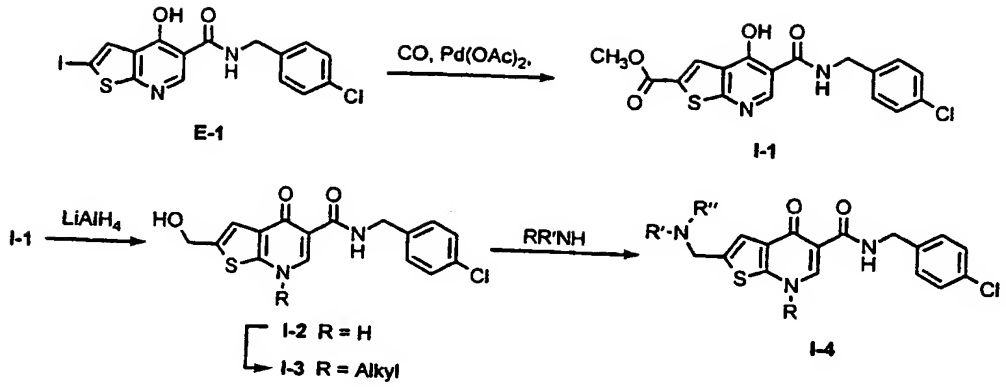


Chart J.

N-(4-Chlorobenzyl)-4-hydroxythieno[2,3-*b*]pyridine-5-carboxamide (A-6 where R = H) undergoes a Mannich reaction by heating with morpholine and formaldehyde in acetic acid/ethanol to afford 2-morpholinomethyl derivative J-1. Compound J-1 is then treated with an optionally substituted alkyl halide in the presence of potassium carbonate or with an optionally substituted alcohol under Mitsunobu conditions to yield thienopyridones of the general formula J-2.

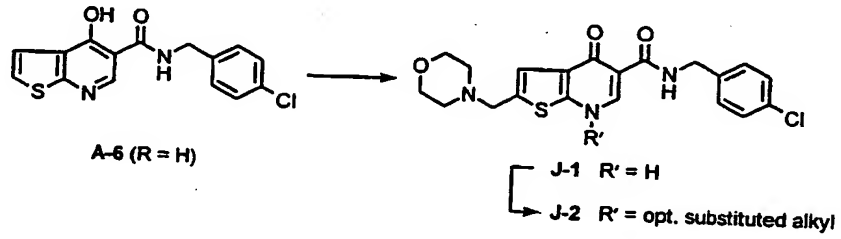


Chart K.

2-Iodothienopyridine-5-carboxamide E-1 undergoes palladium catalyzed carbon monoxide insertion with trapping by an amine to afford 2-carboxamides of the general formula K-1. Compounds K-1 are then treated with an optionally substituted alkyl halide in the presence of potassium carbonate to yield thienopyridones of the formula K-2.

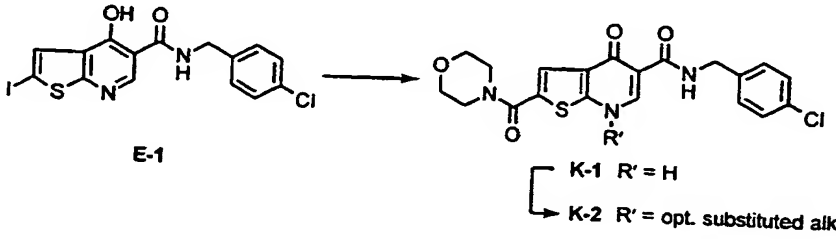


Chart L.

(b) aryl;

(c) C_{3-8}cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R^{11}, NR^7R^8, SO_mR^9, and C_{1-7}alkyl optionally substituted by R^{11}, NR^7R^8, and SO_mR^9; or

(d) *tert*-butyl,

are prepared as exemplified in Chart M. Intermediates bearing the 4-oxo-4,7-dihydrothieno[2,3-b]pyridine ring system are prepared in a manner analogous to that precedent in the literature (M. M. El-Abedelah, M. Z. Nazer, S. F. Okasha, M. Calas, J. Bompart, P. Mion *Eur. J. Med. Chem.* **1998**, *33*, 33-42; and M. M. El-Abedelah, S. S. Sabri, A. A. Al-Ashqar *Hetrocycles* **1997**, *45*, 255-264). 2-Bromo-5-chloro-4-thiophenecarboxylic acid (M-1) (prepared as described by S. Ol, H. Nagaya, N. Inatomi, M. Nakao, H. Yukimasa **WO-97/11705**, 1997) is activated with 1,1′-carbonyldiimidazole and is then treated with ethyl trimethylsilyl malonate in the presence of DBU to afford 3-ketoester M-2. Refluxing compound M-2 in acetic anhydride and triethylorthoformate provides enol ether M-3. Compound M-3 is then contacted with a nitrogen containing compound of the formula RNH_2 where R may be, but is not limited to, the R^2 definition above (e.g., cyclopropylamine, *tert*-butylamine, aniline, 3-furylamine, 4-aminomorpholine, 1-amino-4-methylpiperazine, or *O*-ethylhydroxylamine) to afford a compound of formula M-4. The reaction can conveniently be carried out in ethanol. The resulting enamines M-4 are then cyclized by heating with sodium hydride (or other appropriate base) in tetrahydrofuran to afford the thieno[2,3-*b*]pyridine-5-carboxylic esters of formula M-5. The esters M-5 are heated in the presence of a substituted benzylamine (e.g., 4-chlorobenzylamine) and iodine to afford the corresponding carboxamides of the formula M-6. Alternatively, carboxamides of formula M-6 are prepared such that the esters M-5 are saponified in the presence of aqueous sodium hydroxide affording the corresponding carboxylic acid which is then coupled with a substituted benzylamine in the presence of 1,1′-carbonyldiimidazole. Compounds of the formula M-6 are transformed to derivatives in analogous fashion to that described in charts G and K. Specifically, compounds of formula M-6 are coupled with propargylic alcohol in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and diethylamine to afford compounds of the formula M-7. Saturation of the alkynyl functionality present in M-7 by hydrogenation over a palladium catalyst provides compounds of the formula M-8.

α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, hydrobromide, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Compounds of the present invention can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable excipient, the composition being useful in combating viral infections. Pharmaceutical compositions containing a compound appropriate for antiviral use are prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975). The compounds and compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), topically, orally, or rectally, depending on whether the preparation is used to treat internal or external viral infections.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise

preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

μl volume with 5.4 mM HEPES (pH 7.5), 11.7 mM KCl, 4.5 mM $MgCl_2$, 0.36 mg/ml BSA, and 90 nM ^{3}H-dTTP. Assays are run with and without CHAPS, (3-[(3-cholamidopropyl)-dimethylammonio]-1-propane-sulfonate) at a final concentration of 2 mM. HCMV polymerase is diluted in enzyme dilution buffer containing 50% glycerol, 250 mM NaCl, 10 mM HEPES (pH 7.5), 100 μg/ml BSA, and 0.01% sodium azide. The HCMV polymerase, which is expressed in recombinant baculovirus-infected SF-9 cells and purified according to literature procedures, is added at 10% (or 10 μl) of the final reaction volume, i.e., 100 μl. Compounds are diluted in 50% DMSO and 10 μl are added to each well. Control wells contain an equivalent concentration of DMSO. Unless noted otherwise, reactions are initiated via the addition of 6 nM biotinylated poly(dA)-oligo(dT) template/primer to reaction mixtures containing the enzyme, substrate, and compounds of interest. Plates are incubated in a 25 C or 37 C H_2O bath and terminated via the addition of 40 μl/reaction of 0.5 M EDTA (pH 8) per well. Reactions are terminated within the time-frame during which substrate incorporation is linear and varied depending upon the enzyme and conditions used, i.e., 30 min. for HCMV polymerase. Ten μl of streptavidin-SPA beads (20 mg/ml in PBS/10% glycerol) are added following termination of the reaction. Plates are incubated 10 min. at 37 °C, then equilibrated to room temperature, and counted on a Packard Topcount. Linear regressions are performed and IC_{50}'s are calculated using computer software.

A modified version of the above HCMV polymerase assay is performed as described above, but with the following changes: Compounds are diluted in 100% DMSO until final dilution into assay buffer. In the previous assay, compounds are diluted in 50% DMSO. 4.5 mM dithiotherotol (DTT) is added to the polymerase buffer. Also, a different lot of CMV polymerase is used, which appears to be more active resulting in a more rapid polymerase reaction. Results of the testing of representative compounds of formula I in this assay are shown in Table 1. In Table 1, the term "*nd*" refers to activity data not determined.

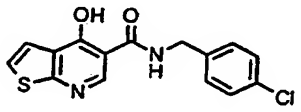
Table 1. Biological Data (continued)

Example	polymerase IC_{50} (μM)		
	HCMV	HSV	VZV
37	*nd*	*nd*	*nd*
38	2.6	*nd*	*nd*
39	< 0.31	*nd*	*nd*
40	< 0.31	*nd*	*nd*
41	3.4	*nd*	*nd*
42	1.9	*nd*	*nd*
43	1.9	*nd*	*nd*
44	4.7	*nd*	*nd*
45	2.6	*nd*	*nd*
46	3.8	*nd*	*nd*
47	> 20.0	*nd*	*nd*
48	19.0	*nd*	*nd*
49	3.2	*nd*	*nd*
50	3.8	*nd*	*nd*
51	1.2	*nd*	*nd*
52	1.5	*nd*	*nd*
53	4.0	*nd*	*nd*
54	3.2	*nd*	*nd*
55	5.0	*nd*	*nd*

nd = not determined.

DESCRIPTION OF PREFERRED EMBODIMENTS

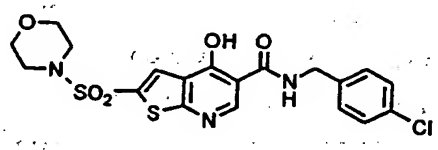
EXAMPLE 1. *N*-(4-Chlorobenzyl)-4-hydroxythieno[2,3-*b*]pyridine-5-carboxamide



A mixture of ethyl 4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate (*J. Heterocyclic Chem.* 1977, *14*, 807) (0.447 g) and 4-chlorobenzylamine (2.43 mL) is stirred at 190 °C for 1 h. The reaction is then allowed to cool to rt and is diluted with toluene (5 mL). The resulting precipitate is filtered off and washed with toluene followed by hexanes to yield an off-white solid. This material is recrystallized from acetic acid/water then ethanol to yield 0.285 g (45%) of the title compound as a white solid.

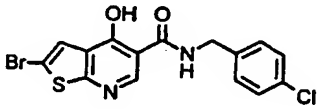
Physical characteristics are as follows:

EXAMPLE 3. *N*-(4-Chlorobenzyl)-4-hydroxy-2-(4-morpholinylsulfonyl)-thieno[2,3-*b*]pyridine-5-carboxamide



(FAB) *m/z* 468 (MH^+); HRMS (FAB) found 468.0458; Anal. Found: C, 48.69; H, 4.10; N, 8.91; Cl, 7.51; S, 13.76.

EXAMPLE 4. 2-Bromo-*N*-(4-chlorobenzyl)-4-hydroxythieno[2,3-*b*]pyridine-5-carboxamide

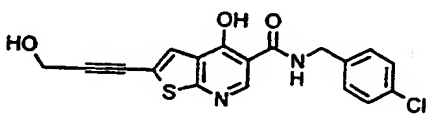


To a solution of ethyl 4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate (*J. Heterocyclic Chem.* **1977**, *14*, 807) (1.00 g) in $CHCl_3$ (26 mL) is added bromine (0.23 mL) dropwise. The reaction is stirred at rt for 2 h. The reaction mixture is poured into 2N HCl (30 mL), and the aqueous layer is extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers are washed with H_2O (100 mL), dried with $MgSO_4$, filtered and concentrated in vacuo to yield 0.840 g (62%) of the bromide as a yellow solid. This material (0.757 g) is suspended in 10% aqueous NaOH (7 mL) and heated to reflux. The reaction is stirred at reflux for 1 h. The reaction mixture is cooled to rt, and H_2O (26 mL) is added. Conc. HCl is added until a precipitate forms. The precipitate is filtered off to yield 0.597 (87%) of the acid as a brown solid. Carbonyldiimidazole (0.530 g) is added to a solution of 2-bromo-4-hydroxy-thieno-[2,3-*b*]pyridine-5-carboxylic acid (0.597 g) in DMF (20 mL). The reaction is heated to 60 °C and stirred for 18 h. The reaction mixture is cooled to rt, and 4-chloro-benzylamine (1.01 mL) is added. The reaction is stirred at rt for 7 h. The reaction mixture is poured into 20% aqueous HOAc (180 mL), and the resulting white solid is filtered off. This material is recrystallized from methanol then toluene to yield 2.095 g (74%) of the title compound as a white solid.

Physical characteristics are as follows:

Mp 234-236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.25, 10.41, 8.74, 7.52, 7.41-7.33, 4.53; ^{13}C NMR (75 MHz, TFA) δ 167.7, 166.9, 153.9, 139.1, 134.7, 133.2, 129.0, 128.9, 128.1, 122.3, 116.7, 108.6, 43.8; IR (drift) 3187, 3098, 3074, 3024, 2927, 2842, 1645, 1592, 1541, 1503, 1338, 1287, 916, 792, 689 cm^{-1}; MS (ESI-) *m/z* 397 $(M-H)^-$; Anal. Found: C, 45.03; H, 2.73; N, 6.98; Br, 19.72; Cl, 8.70; S, 7.96.

EXAMPLE 5. *N*-(4-Chlorobenzyl)-4-hydroxy-2-(3-hydroxy-1-propynyl)thieno-[2,3-*b*]pyridine-5-carboxamide

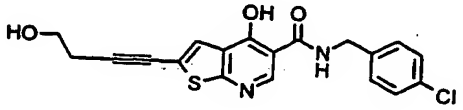


concentrated in vacuo to yield to yield 0.260 g (30%) of the title compound as an off-white solid.

Physical characteristics are as follows:

Mp 215-218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.33, 10.40, 8.76, 7.56, 7.41-7.33, 4.55, 3.33; ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.8, 143.1, 139.0, 131.9, 129.6, 128.8, 127.6, 116.4, 114.2, 92.5, 78.7, 60.0, 57.7, 41.9; IR (drift) 3176, 3074, 3016, 2924, 2859, 2822, 2320, 2218, 1640, 1587, 1534, 1512, 1353, 1097, 783 cm^{-1}; MS (ESI-) for *m/z* 385 $(M-H)^-$; Anal. Found: C, 58.84; H, 4.09; N, 7.28; Cl, 9.16; S, 8.32.

EXAMPLE 7. *N*-(4-Chlorobenzyl)-4-hydroxy-2-(4-hydroxy-1-butynyl)thieno[2,3-*b*]pyridine-5-carboxamide



To a suspension of *N*-(4-chlorobenzyl)-4-hydroxy-2-iodothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 2) (1.00 g) in diethylamine (28 mL) is added copper iodide (0.128 g) and $Pd(PPh_3)_2Cl_2$ (0.032 g) followed by addition of 3-butyn-1-ol (0.20 mL). The reaction is stirred at rt for 18 h. The reaction mixture is partitioned between H_2O (100 mL) and ethyl acetate (100 mL). The organic layer is removed, and the aqueous layer is extracted with ethyl acetate (2 x 100 mL). Combined organic layers are dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting brown oil is purified via column chromatography (CH_2Cl_2:CH_3OH; 98:2). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield a brown solid. This material is dissolved in DMF (15 mL) and 2N HCl is added until a precipitate forms. The resulting tan solid is purified via column chromatography (CH_2Cl_2:CH_3OH; 98:2, 95:5). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield 0.183 g (21%) of the title compound as a yellow, crystalline solid.

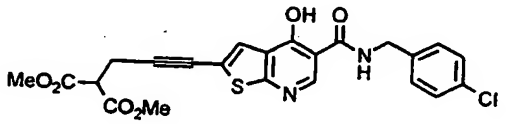
Physical characteristics are as follows:

Mp 242-246 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.31, 10.43, 8.73, 7.41-7.33, 4.95, 4.54, 3.59, 2.62; IR (drift) 2934, 2915, 2845, 2771, 2352, 2327, 2224, 1965, 1920, 1662, 1646, 1587, 1538, 1515, 1500 cm^{-1}; MS (ESI-) for *m/z* 385 $(M-H)^-$. Anal. Found: C, 58.61; H, 4.05; N, 7.18; Cl, 9.02; S, 8.11.

EXAMPLE 8. *N*-(4-Chlorobenzyl)-4-hydroxy-2-(3-hydroxypropyl)thieno[2,3-*b*]pyridine-5-carboxamide

1638, 1587, 1524, 1484, 1398, 1342, 1298, 884, 791 cm $^{-1}$; HRMS (EI) found 343.1082; Anal. Found: C, 55.31; H, 2.88; N, 12.02; Cl, 9.95; S, 9.04.

EXAMPLE 10. Dimethyl 2-[3-(5-{[(4-chlorobenzyl)amino]carbonyl}-4-hydroxythieno[2,3-*b*]pyridin-2-yl)-2-propynyl]malonate

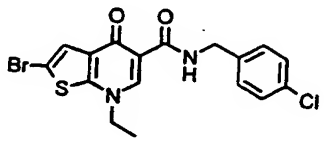


To a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-iodothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 2) (0.500 g) in diethylamine (14 mL) and DMF (1.5 mL) is added copper iodide (0.064 g) and $Pd(PPh_3)_2Cl_2$ (0.039 g) followed by addition of dimethyl propargyl malonate (0.24 mL). The reaction is stirred at rt for 18 h. The reaction mixture is concentrated in vacuo. The resulting orange solid is purified via column chromatography (CH_2Cl_2:CH_3OH; 98:2). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield an orange solid which is recrystallized twice from methanol to yield 0.267 g (49%) of the title compound as an off-white solid.

Physical characteristics are as follows:

Mp 197-198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.30, 10.40, 8.74, 7.41-7.33, 4.54, 3.94, 3.71, 3.01; ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.5, 139.0, 131.9, 129.6, 128.8, 126.6, 93.2, 74.8, 53.2, 50.3, 41.9, 19.6; IR (drift) 2353, 2327, 2229, 1738, 1663, 1646, 1593, 1568, 1540, 1516, 1491, 1435, 1347, 1286, 1240 cm $^{-1}$; MS (FAB) m/z 487 (MH+, 99), 973 (7), 490 (12), 489 (43), 488 (37), 487 (99), 486 (21), 346 (27), 140 (13), 127 (14), 125 (41); HRMS (FAB) found 487.0714; Anal. Found: C, 56.46; H, 3.80; N, 5.74; Cl, 7.32; S, 6.55 (corrected for 3.10% H_2O).

EXAMPLE 11. 2-Bromo-*N*-(4-chlorobenzyl)-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide



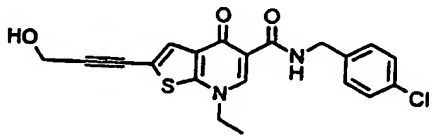
A mixture of ethyl 2-bromo-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate (*Eur. J. Med. Chem.* **1987**, *22*, 139) (0.500 g) and 4-chlorobenzylamine (1.84 mL) is stirred at 190 °C for 1 h. The reaction is then allowed to cool to rt and is diluted with toluene. The resulting precipitate is filtered off and washed with toluene followed by

Carbonyldiimidazole (0.290 g) is added to a solution of 7-ethyl-2-iodo-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (*Eur. J. Med. Chem.* **1987**, *22*, 139) (0.520 g) in DMF (13 mL). The reaction is heated to 60 °C and stirred for 18 h. The reaction mixture is cooled to rt, and 4-chlorobenzylamine (0.22 mL) is added. The reaction is stirred at rt for 7 h. The reaction mixture is poured into 20% aqueous HOAc (50 mL), and the resulting off-white solid is filtered off. This material is recrystallized twice from methanol to yield 0.372 g (53%) of the title compound as an off-white, crystalline solid.

Physical characteristics are as follows:

Mp 214-218 °C; ^{1}H NMR (300 MHz, DMSO- d_6) δ 10.45, 8.72, 7.71, 7.41-7.33, 7.53, 4.30, 1.42; ^{13}C NMR (75 MHz, TFA) δ 166.4, 165.9, 158.7, 141.5, 134.9, 133.1, 131.0, 129.7, 129.1, 129.0, 110.2, 108.8, 77.4, 56.0, 44.0, 12.4; IR (drift) 1654, 1590, 1541, 1511, 1489, 1431, 1408, 1295, 1217, 1086, 1014, 851, 800, 794, 707, cm^{-1}; MS (ESI+) *m/z* 473 $(M+H)^+$; Anal. Found: C, 42.80; H, 3.00; N, 5.82; Cl, 7.51; S, 6.85.

EXAMPLE 14. *N*-(4-Chlorobenzyl)-7-ethyl-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide



To a suspension of *N*-(4-chlorobenzyl)-7-ethyl-2-iodo-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 12) (0.267 g) in diethylamine (14 mL) is added copper iodide (0.032 g) and $Pd(PPh_3)_2Cl_2$ (0.009 g) followed by addition of propargyl alcohol (39 μL). The reaction is stirred at rt for 18 h. The diethylamine is removed in vacuo, and the resulting residue is partitioned between H_2O (25 mL) and CH_2Cl_2 (25 mL). The organic layer is removed, and the aqueous layer is extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers are dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting orange solid is purified by column chromatography (CH_2Cl_2:CH_3OH, 98:2). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield 0.158 g (70%) of the title compound as a yellow, crystalline solid.

Physical characteristics are as follows:

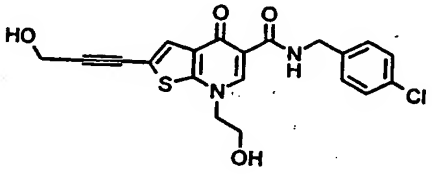
Mp 217-219 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41, 8.79, 7.53, 7.41-7.33, 5.47, 4.54, 4.36, 4.29, 1.44; ^{13}C NMR (75 MHz, DMSO- d_6) δ 172.3, 164.4, 149.7, 145.5, 138.9, 131.9, 131.5, 129.6, 128.8, 128.0, 116.9, 115.6, 96.9, 76.2, 52.4, 50.0, 41.9, 14.2; IR (drift) 3390, 2478, 2339, 2284, 2040, 1915, 1655, 1591, 1544, 1502, 1300, 1224, 1029, 1015, 795, cm^{-1}; MS (ESI+) *m/z* 399 $(M+H)^+$; Anal. Found: C, 59.42; H, 4.35; N, 6.88; Cl, 8.85; S, 7.98.

reaction mixture is filtered through a Celite pad, and the filtrate is concentrated in vacuo. The resulting yellow solid is purified via column chromatography (CH_2Cl_2, CH2Cl2:CH_3OH; 98:2, 95:5). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield 0.114 g (57%) of the title compound as a white solid.

Physical characteristics are as follows:

Mp 144-146 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62, 8.72, 7.41-7.33, 7.20, 4.56, 4.55, 4.31, 3.47, 2.90, 1.80, 1.44; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 164.8, 148.6, 144.2, 140.5, 139.1, 132.1, 131.8, 129.6, 128.8, 120.0, 115.1, 60.0, 52.1, 41.9, 34.3, 26.5, 14.4; IR (drift) 3055, 2929, 2352, 1916, 1654, 1594, 1551, 1544, 1507, 1491, 1299, 1230, 1092, 801, 708 cm^{-1}; MS (ESI-) for *m/z* 403 (M-H)$^-$; Anal. Found: C, 59.61; H, 5.38; N, 6.75; Cl, 8.51; S, 7.61.

EXAMPLE 17. *N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide



To a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(3-hydroxy-1-propynyl)thieno[2,3-*b*]pyridine-5-carboxamide (Example No. 5) (0.250 g) in DMF (3 mL) is added K_2CO_3 (0.278 g) and 2-bromoethanol (0.14 mL). The reaction is heated to 100 °C and stirred for 18 h. The reaction mixture is concentrated in vacuo, and the resulting residue is partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer is extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers are dried with $MgSO_4$, filtered, and concentrated in vacuo to give a small amount of starting material. The desired product precipitates out of the aqueous layer as a tan solid. This material is recrystallized from methanol to yield 0.100 g (36%) of the title compound as a tan, crystalline solid.

Physical characteristics are as follows:

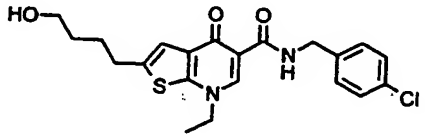
Mp 231-234 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43, 8.70, 7.56, 7.42-7.33, 5.46, 5.16, 4.55, 4.36, 4.31, 3.82; ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.4, 167.0, 152.9, 149.0, 114.3, 134.2, 133.8, 132.0, 131.2, 130.1, 119.1, 117.3, 99.1, 78.5, 62.1, 52.3, 44.2; IR (drift) 3381, 3228, 2395, 2218, 1905, 1646, 1591, 1555, 1505, 1341, 1079, 1026, 848, 800, 602 cm^{-1}; HRMS (EI) found 416.0596; Anal. Found: C, 56.62; H, 3.99; N, 6.52; Cl, 8.35; S, 7.52.

To a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(3-hydroxy-1-propynyl)-thieno[2,3-*b*]pyridine-5-carboxamide (Example No. 5) (0.250 g) in DMF (3 mL) is added K_2CO_3 (0.278 g) and bromoacetic acid (0.279 g). The reaction is heated to 100 °C and stirred for 18 h. An additional 0.200 g of bromoacetic acid is added and the reaction is stirred for an additional 18 h. The reaction mixture is concentrated in vacuo, and the resulting residue is dissolved in 10% NaOH and washed with CH_2Cl_2. The aqueous layer is acidified with conc. HCl and the resulting precipitate is filtered. This material is recrystallized 3 times from methanol to yield 0.068 g (24%) of the title compound as a tan solid.

Physical characteristics are as follows:

Mp 230-235 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.85, 10.34, 8.83, 7.57, 7.42-7.33, 5.48, 5.45, 4.56, 4.34; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.4, 168.5, 164.2, 150.9, 147.3, 138.9, 131.9, 131.1, 129.6, 128.9, 127.8, 116.9, 115.5, 97.0, 76.0, 57.0, 50.0, 42.0; IR (drift) 3362, 3279, 2342, 2223, 1726, 1639, 1581, 1551, 1505, 1416, 1243, 1222, 1208, 1027, 801 cm^{-1}; MS (FAB) m/z (rel. intensity) 431 (MH+, 99), 433 (39), 432 (26), 431 (99), 290 (20), 125 (34), 121 (21), 119 (13), 81 (11), 63 (23), 49 (24); HRMS (FAB) found 431.0474; Anal. Found: C, 52.52; H, 3.33; N, 6.08; Cl, 9.90; S, 7.10.

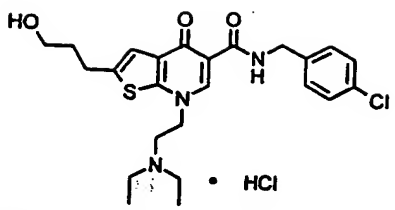
EXAMPLE 20. *N*-(4-chlorobenzyl)-7-ethyl-2-(4-hydroxybutyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide



A solution of *N*-(4-chlorobenzyl)-7-ethyl-2-(4-hydroxy-1-butynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 15) (0.257 g) in 1/1 CH_2Cl_2/CH_3OH (50 mL) is hydrogenated over 10% Pd/C (75 mg) at 35 psi for 2 h. The reaction mixture is filtered through a Celite pad, and the filtrate is concentrated in vacuo. The resulting pale yellow solid is purified via column chromatography (CH_2Cl_2:CH_3OH; 98:2). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield 0.209 g (81%) of the title compound as a white solid.

Physical characteristics are as follows:

Mp 136-139 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60, 8.72, 7.41-7.33, 7.20, 4.55, 4.42, 4.31, 3.44, 2.88, 1.69, 1.49, 1.44; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3,

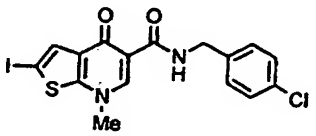


To a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(3-hydroxypropyl)thieno[2,3-*b*]pyridine-5-carboxamide (Example No. 8) (0.300 g) in DMF (4 mL) are added K_2CO_3 (0.550 g) and 2-bromo-*N*,*N*-diethylethylamine hydrobromide (0.623 g). The reaction is heated to 90 °C and stirred for 3 d. An additional 0.220 g of K_2CO_3 and 0.415 g of 2-bromo-N,*N*-diethylethylamine hydrobromide are added. The reaction is stirred at 90 °C for 6 h. The reaction mixture is concentrated in vacuo, and the resulting residue is partitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). The aqueous layer is extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers are dried with $MgSO_4$, filtered and concentrated in vacuo. The resulting yellow oil is purified via column chromatography (CH_2Cl_2:CH_3OH; 98:2, 95:5). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield a yellow oil. This material is dissolved in methanolic HCl and then concentrated in vacuo. The residue is recrystallized twice from ethyl acetate/methanol to yield 0.078 g (19%) of the title compound as an off-white, crystalline solid.

Physical characteristics are as follows:

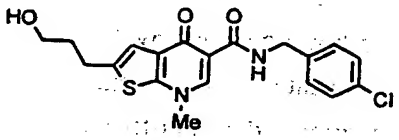
Mp 111-114 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.93, 10.53, 8.82, 7.42-7.33, 7.21, 4.76, 4.56, 3.55, 3.42, 3.22, 2.92, 1.83, 1.28; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5, 164.6, 149.0, 145.5, 140.6, 139.1, 132.1, 131.9, 129.6, 128.8, 120.2, 115.4, 60.0, 50.7, 48.7, 47.2, 41.9, 34.4, 26.5, 8.9; IR (drift) 2350, 2350, 2338, 2329, 2250, 1941, 1656, 1596, 1537, 1507, 1489, 1459, 1451, 1011, 799 cm^{-1}; MS (FAB) *m/z* 476 (MH^+); HRMS (FAB) found 476.1792; Anal. Found: C, 55.44; H, 6.27; N, 8.01; Cl, 13.90; S, 6.24 (corrected for 6.35% H_2O).

EXAMPLE 23. *N*-(4-chlorobenzyl)-2-iodo-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide



To a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-iodothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 2) (2.00 g) in DMF (14 mL) are added K_2CO_3 (1.76 g) and

EXAMPLE 25. *N*-(4-Chlorobenzyl)-2-(3-hydroxypropyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide

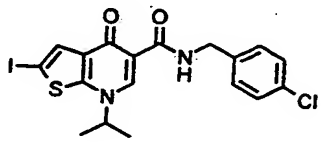


A solution of *N*-(4-chlorobenzyl)-2-(3-hydroxy-1-propynyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 24) (0.520 g) in 1/1 CH_2Cl_2/ethanol (160 mL) is hydrogenated over 10% Pd/C (0.156 g) at 35 psi for 2 h. The reaction mixture is filtered through a Celite pad, and the filtrate is concentrated in vacuo. The resulting pale yellow solid is purified via column chromatography (CH_2Cl_2:CH_3OH; 98:2). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield a pale yellow solid (this material contains a small amount of partially reduced product). This material is dissolved in ethanol (100 mL) and hydrogenated over 10% Pd/C (0.156 g) at 35 psi for 1 h. The reaction mixture is filtered through a Celite pad, and the filtrate is concentrated in vacuo. The resulting off-white solid is recrystallized from ethanol to yield 0.211 g (40%) of the desired product as an off-white solid.

Physical characteristics are as follows:

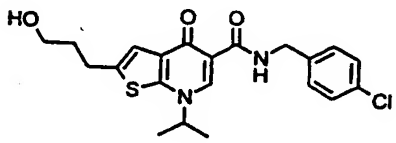
Mp 197-198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61, 8.69, 7.41-7.33, 7.21, 4.58-4.53, 3.95, 3.47, 2.91, 1.80; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 164.9, 149.8, 145.5, 140.6, 139.1, 131.8, 131.5, 129.6, 128.8, 120.0, 114.7, 60.0, 43.4, 41.9, 34.4, 26.5; IR (drift) 3052, 1921, 1653, 1596, 1557, 1512, 1489, 1429, 1305, 1242, 1091, 1032, 801, 727, 712 cm^{-1}; HRMS (FAB) found 391.0904; Anal. Found: C, 57.42; H, 4.78; N, 7.03; Cl, 8.78; S, 8.13.

EXAMPLE 26. *N*-(4-Chlorobenzyl)-2-iodo-7-isopropyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide



To a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-iodothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 2) (2.00 g) in DMF (14 mL) are added K_2CO_3 (1.76 g) and 2-bromopropane (1.19 mL). The reaction is heated to 90 °C and stirred for 18 h. The

EXAMPLE 28. *N*-(4-Chlorobenzyl)-2-(3-hydroxypropyl)-7-isopropyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide

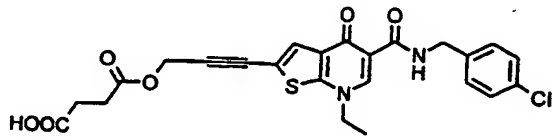


A solution of *N*-(4-chlorobenzyl)-2-(3-hydroxy-1-propynyl)-7-isopropyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 27) (0.225 g) in ethanol (50 mL) is hydrogenated over 10% Pd/C (68 mg) at 35 psi for 2 h. The reaction mixture is filtered through a Celite pad, and the filtrate is concentrated in vacuo. The resulting pale yellow solid is recrystallized from ethyl acetate/heptane to yield 0.104 g (46%) of the desired product as an off-white solid.

Physical characteristics are as follows:

Mp 84-92 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61, 8.66, 7.41-7.33, 7.21, 4.59-4.50, 3.47, 2.91, 1.80, 1.57; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 164.8, 148.6, 140.4, 140.0, 139.1, 132.2, 131.9, 129.7, 128.8, 120.0, 115.1, 60.0, 59.0, 41.9, 34.3, 26.4, 21.5; IR (drift) 3491, 1660, 1594, 1538, 1504, 1465, 1448, 1349, 1325, 1294, 1216, 1090, 1060, 1012, 798 cm^{-1}; MS (FAB) m/z 419 (MH^+); HRMS (FAB) found 419.1172; Anal. Found: C, 60.06; H, 5.52; N, 6.58; Cl, 8.27; S, 7.57.

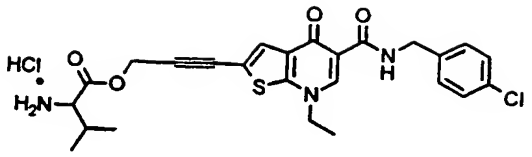
EXAMPLE 29. 4-{[3-(5-{[(4-chlorobenzyl)amino]carbonyl}-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-2-propynyl]oxy}-4-oxobutanoic acid



To a solution of *N*-(4-chlorobenzyl)-7-ethyl-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 14) (0.200 g) in pyridine (10 mL) is added succinic anhydride (0.639 g). The reaction is stirred at rt for 18 h then at 40 °C for 1 h. The reaction mixture is concentrated in vacuo. The residue is suspended in H_2O (25 mL) and stirred for 1 h. An off-white solid is filtered off and recrystallized from ethanol to yield 0.210 g (84%) of the title compound as a pale yellow, crystalline solid.

Physical characteristics are as follows:

Mp 180-182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.27, 10.38, 8.80, 7.65, 7.41-7.33, 5.02, 4.54, 4.31, 2.62-2.50, 1.44; ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 172.3,

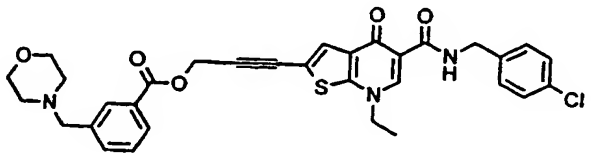


To a solution of *N*-(4-chlorobenzyl)-7-ethyl-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Example No. 14) (0.400 g) in pyridine (16 mL) are added EDC (0.288 g), DMAP (0.020 g), and *N*-Boc valine (0.326 g). The reaction is stirred at rt for 3 d. The reaction mixture was concentrated in vacuo. The residue is dissolved in CH_2Cl_2 (80 mL), washed with H_2O (40 mL) and brine (40 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow solid is recrystallized from ethanol to yield 0.492 g (82%) of the Boc-protected compound. This material (0.303 g) is dissolved in CH_2Cl_2 (6 mL) and cooled to 0 °C. Trifluoroacetic acid (6 mL) is added, and the reaction is stirred at 0 °C for 1 h. The reaction mixture is concentrated in vacuo. The resulting residue is dissolved in CH_2Cl_2 (60 mL), washed with saturated aqueous $NaHCO_3$ (60 mL) and H_2O (60 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting white solid is recrystallized from ethanol to yield 0.128 g (51%) of the free amine as a white, crystalline solid. The amine (0.105 g) is dissolved in methanolic HCl (4 mL) and concentrated in vacuo. The resulting residue is recrystallized from methanol/ethyl acetate to yield 0.092 g (81%) of the title compound as a white solid.

Physical characteristics are as follows:

Mp 171-172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36, 8.81, 8.52, 7.66, 7.42-7.33, 5.22, 4.55, 4.33, 4.02, 2.22, 1.44, 1.01; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 169.0, 164.2, 150.3, 145.8, 138.9, 131.9, 131.3, 129.6, 129.5, 128.8, 115.7, 115.3, 90.1, 79.0, 57.6, 54.1, 52.5, 42.0, 30.0, 18.7, 18.0, 14.2; IR (drift) 3047, 2968, 2935, 2914, 2879, 2226, 1931, 1754, 1649, 1594, 1544, 1502, 1232, 1212, 803 cm^{-1}; MS (FAB) m/z 500 (MH^+); HRMS (FAB) found 500.1408; Anal. Found: C, 54.10; H, 5.06; N, 7.55; Cl, 12.77; S, 5.81.

EXAMPLE 32. 3-(5-{[(4-Chlorobenzyl)amino]carbonyl}-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-2-propynyl 3-(4-morpholinylmethyl)benzoate

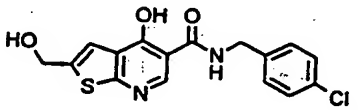


and desired product is isolated as a yellow solid. This material is re-subjected to the reaction conditions above. The reaction is stirred at 70 °C for 18 h. The reaction is cooled to rt and water (25 mL) and 2 N HCl (25 mL) are added. The resulting orange solid is filtered off and purified by column chromatography (CH_2Cl_2; CH_2Cl_2/methanol, 99/1; 98/2). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield a pale yellow solid which is recrystallized from methanol to yield 1.337 g (60%) of the title compound as a pale yellow, crystalline solid.

Physical characteristics are as follows:

Mp 238-240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.45, 10.30, 8.80, 7.96, 7.41-7.33, 4.55, 3.87; ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.3, 164.1, 161.7, 151.4, 143.5, 138.5, 131.4, 130.6, 129.1, 128.3, 127.9, 126.4, 114.0, 52.7, 41.4; IR (drift) 2944, 2350 (w), 1729, 1645, 1595, 1549, 1543, 1485, 1478, 1433, 1284, 1238, 1175, 800, 751 cm^{-1}; MS (ESI-) for *m/z* 375 $(M-H)^-$. Anal. Found (corrected for 3.64% H_2O): C, 54.03; H, 3.38; N, 7.39; Cl, 9.41; S, 8.52.

EXAMPLE 34. *N*-(4-Chlorobenzyl)-4-hydroxy-2-(hydroxymethyl)thieno[2,3-*b*]pyridine-5-carboxamide.



Methyl 5-{[(4-chlorobenzyl)amino]carbonyl}-4-hydroxythieno[2,3-*b*]pyridine-2-carboxylate (0.506 g) from Example No. 33 is dissolved in THF (100 mL) with heating and then the reaction is cooled in an ice bath. To this solution is added a 1.0 M solution of $LiAlH_4$ in THF (2.4 mL). The reaction is allowed to warm to room temperature and is stirred for 2.5 h. The reaction is quenched with water (1 mL), 10% NaOH (1 mL), and H_2O (1 mL). The aluminum salts are filtered off and the filtrate is concentrated in vacuo. The resulting yellow oil is purified by column chromatography (CH_2Cl_2/methanol, 98/2; 95/5). Fractions homogeneous by TLC are combined and concentrated in vacuo to yield 0.254 g (54%) of the title compound as a pale yellow solid.

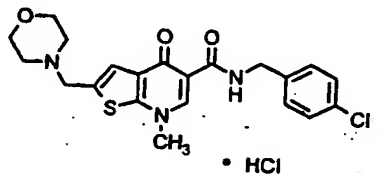
Physical characteristics are as follows:

Mp 205-210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.34, 10.57, 8.66, 7.41-7.33, 7.22, 5.69, 4.68, 4.54; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.4, 164.9, 148.5, 141.8, 141.4, 138.6, 131.4, 130.5, 129.2, 128.3, 117.3, 113.2, 58.5, 48.6, 41.4; IR (drift) 3007, 2917, 2854, 2319, 1903, 1647, 1593, 1568, 1538, 1511, 1493, 1353, 1298, 1123, 789 cm^{-1}; MS (ESI-) for *m/z* 347 $(M-H)^-$. Anal. Found: C, 54.86; H, 3.89; N, 7.86; Cl, 10.00; S, 9.01.

Physical characteristics are as follows:

Mp 230-236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59, 8.70, 7.41-7.32, 4.55, 3.96, 3.59, 2.45; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 165.0, 150.6, 144.5, 138.1, 137.4, 132.8, 131.6, 128.9, 128.7, 121.3, 115.8, 66.9, 57.7, 53.5, 43.1, 42.6; IR (drift) 2815, 1906, 1654, 1597, 1544, 1511, 1491, 1456, 1306, 1112, 865, 811, 806, 798, 729, cm^{-1}; MS (ESI+) for m/z 432 $(M+H)^+$. Anal. Found: C, 57.99; H, 5.20; N, 9.60; Cl, 8.23; S, 7.34.

EXAMPLE 37. *N*-(4-Chlorobenzyl)-7-methyl-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide hydrochloride.



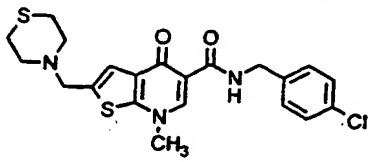
• HCl

N-(4-chlorobenzyl)-7-methyl-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (1.50 g) from Example No. 36 is dissolved in methanolic HCl (50 mL) and concentrated in vacuo. The resulting off-white solid is recrystallized from methanol/ethanol to yield 1.458 g (90%) of the title compound as a white solid.

Physical characteristics are as follows:

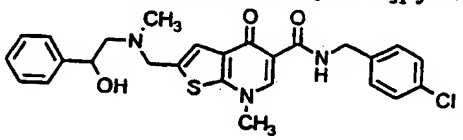
Mp 278-280 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89, 10.47, 8.78, 7.76, 7.42-7.32, 4.66, 4.56, 4.05-3.90, 3.98, 3.85-3.73, 3.38-3.25, 3.18-3.02; ^{13}C NMR (DMSO-d_6) δ 172.1, 164.0, 152.2, 146.1, 138.4, 131.3, 130.3, 129.0, 128.6, 128.2, 124.9, 114.5, 63.1, 52.6, 50.2, 42.9, 41.6; IR (drift) 2464, 2464, 2432, 2414, 2389, 2244, 1666, 1601, 1552, 1510, 1235, 1117, 1080, 804, 795 cm^{-1}; MS (ESI+) *m/z* 432 $(M+H)^+$; Anal. Found: C, 53.82; H, 4.97; N, 8.95; Cl, 15.16; S, 6.84.

EXAMPLE 38. *N*-(4-Chlorobenzyl)-7-methyl-4-oxo-2-(4-thiomorpholinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.



To a solution of *N*-(4-chlorobenzyl)-2-(hydroxymethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (0.300 g) from Example No. 35 in DMF (16 mL) are added DMAP (16 mg), 2,4,6-collidine (0.27 mL), and methanesulfonyl chloride (0.16 mL). The reaction mixture is stirred at room temperature for 2 h and then

EXAMPLE 40. *N*-(4-Chlorobenzyl)-2-(((2-hydroxy-2-phenylethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.

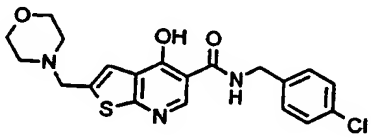


To a solution of *N*-(4-chlorobenzyl)-2-(hydroxymethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (0.300 g) from Example No. 35 in DMF (17 mL) are added DMAP (16 mg), 2,4,6-collidine (0.27 mL), and methanesulfonyl chloride (0.16 mL). The reaction mixture is stirred at room temperature for 1 h and then α-(methylaminomethyl)benzyl alcohol (1.26 g) is added. The mixture is stirred at room temperature for 18 h and is then poured into water (50 mL). The resulting off-white solid is filtered off and purified by column chromatography (CH_2Cl_2/methanol, 99/1; 97/3) to yield 0.261 g (63%) of the title compound as a pale yellow solid.

Physical characteristics are as follows:

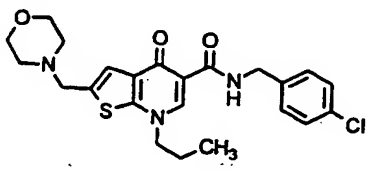
Mp 184-187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61, 8.69, 7.41-7.21, 5.17, 4.79-4.73, 4.55, 3.92, 3.86, 2.69-2.50, 2.31; ^{13}C NMR (DMSO-d_6) δ 171.8, 164.3, 150.3, 145.0, 144.6, 139.6, 138.5, 131.2, 130.4, 129.0, 128.2, 127.7, 126.7, 126.1, 119.9, 114.2, 70.5, 64.6, 56.2, 42.7, 42.2, 41.2; IR (drift) 1652, 1595, 1532, 1490, 1369, 1347, 1336, 1303, 1242, 1130, 1124, 1086, 803, 757, 697 cm^{-1}; MS (ESI+) *m/z* 496 $(M+H)^+$; Anal. Found: C, 63.01; H, 5.40; N, 8.29; Cl, 7.03; S, 6.37.

EXAMPLE 41. *N*-(4-Chlorobenzyl)-4-hydroxy-2-(4-morpholinylmethyl)-thieno[2,3-*b*]pyridine-5-carboxamide.



Formaldehyde (2.6 mL) is added to morpholine (2.7 mL) at 0 °C. Ethanol (10 mL) is then added followed by addition of *N*-(4-chlorobenzyl)-4-hydroxythieno[2,3-*b*]pyridine-5-carboxamide (1.00 g) from Example No. 1. Acetic acid (2 mL) is added, and the reaction mixture is allowed to warm to rt and then refluxed for 18 h. Additional morpholine (2.7 mL) and formaldehyde (2.6 mL) are added and the reaction is refluxed for an additional 24 h. The reaction mixture is allowed to cool to room temperature and is then concentrated in vacuo. The residue is treated with 25% NaOH (20 mL). The aqueous layer is extracted with ethyl acetate (50 mL) then $CHCl_3$ (60 mL). Methanol (30 mL) is added to the aqueous layer and it is extracted with $CHCl_3$ (2 x 60 mL). This procedure is repeated 3 times. The combined organic layers are dried with $MgSO_4$, filtered, and concentrated in vacuo. The

Example 43. *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-propyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.

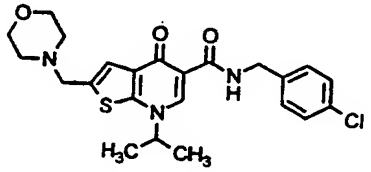


N-(4-Chlorobenzyl)-4-hydroxy-2-(4-morpholinylmethyl)thieno[2,3-*b*]pyridine-5-carboxamide (418 mg) from Example No. 41 and potassium carbonate (152 mg) are suspended in DMF (10 mL) and to the mixture is added 1-iodopropane (107 μL). The reaction mixture is allowed to stir at room temperature for 4 h. Additional 1-iodopropane (107 μL) is added and the mixture is heated to 60 °C for 2 h. The mixture is allowed to cool to room temperature and stand for 18 h. The resulting suspension is poured into water (25 mL), filtered, and washed with water (5 mL) followed by diethyl ether (5 mL). The resulting crude solid is purified by recrystallization from ethanol to afford 335 mg (73%) of the title compound as a white solid.

Physical characteristics are as follows:

Mp 174-176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58, 8.71, 7.42-7.33, 4.54, 4.26, 3.74, 3.59, 2.45, 1.86, 0.90; ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.9, 164.3, 149.6, 144.4, 138.6, 137.9, 131.4, 131.1, 129.1, 128.3, 120.6, 114.4, 66.1, 57.6, 56.6, 52.9, 41.4, 21.6, 10.6; IR (drift) 2968, 1652, 1593, 1540, 1505, 1458, 1351, 1343, 1327, 1300, 1226, 1111, 1014, 865, 808 cm^{-1}; MS (ESI+) *m/z* 460 (100, $(M+H)^+$), 461 (28), 462 (40); HRMS (FAB) *m/z* 460.1461 ($C_{23}H_{26}ClN_3O_3S$+H). Anal. Found ($C_{23}H_{26}ClN_3O_3S$): C, 60.03; H, 5.76; N, 9.11; Cl, 7.75; S, 6.95.

EXAMPLE 44. *N*-(4-Chlorobenzyl)-7-isopropyl-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.



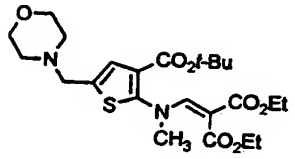
N-(4-Chlorobenzyl)-4-hydroxy-2-(4-morpholinylmethyl)thieno[2,3-*b*]pyridine-5-carboxamide (418 mg) from Example No. 41 and potassium carbonate (152 mg) are suspended in DMF (10 mL) and to the mixture is added 2-bromopropane (103 μL). The reaction mixture is stirred at room temperature for 4 h. Additional 2-bromopropane (103 μL) is added and the mixture is heated to 60 °C for 20 h. The reaction mixture is allowed to cool to room temperature, is poured into water (25 mL), and then extracted with EtOAc

Iodomethane (3.0 ml) is added to a mixture of *N*-(3-*tert*-butoxycarbonyl-thien-2-yl)-aminomethylenemalonic acid diethyl ester (15.0 g) from Preparation No. 1 and anhydrous potassium carbonate (8.4 g) in DMF (67 ml). The mixture is stirred vigorously at ambient temperature for about 20 hr. Water (150 ml) is added and the solution is extracted with toluene (2 x 75 ml). The combined toluene layers are washed with water (2 x 150 ml) and the solvent is removed in vacuo to provide 15.8 g of the title compound as a dark yellow oil.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5, 7.3, 7.2, 4.2, 3.96, 3.36, 1.55, 1.25; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.31, 160.57, 149.37, 128.14, 127.98, 121.42, 99.45, 81.85, 60.87, 60.21, 28.08, 14.27, 13.86.

PREPARATION 3: *N*-(3-*tert*-Butoxycarbonyl-5-morpholinomethyl-thien-2-yl)-methylaminomethylenemalonic Acid Diethyl Ester.



A mixture of *N*-(3-*tert*-butoxycarbonyl-thien-2-yl)-methylaminomethylenemalonic acid diethyl ester (19.0 g) from Preparation No. 2 and 4-methylene morpholinium chloride (Dimmock, JR, et al *Eur. J. Med. Chem.* **1989**, *24*, 379-383) (13.4 g) in dry acetonitrile (50 ml) is heated at reflux for about 4 hr. The solution is then cooled in an ice bath and saturated aqueous sodium carbonate (98 ml) is slowly added. The solution is extracted three times with ethyl acetate (300 ml total) and the combined organic layers are then washed three times with water (600 ml total). The solvents are removed in vacuo to afford 23.0 g (96%) of the title compound as a brown oil.

Physical characteristics are as follows:

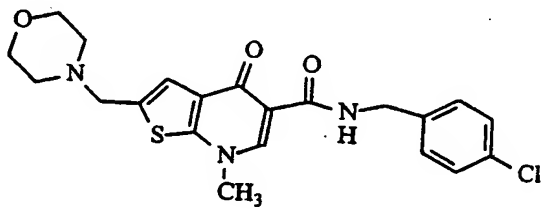
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45, 7.06, 4.1, 3.70, 3.60, 3.34, 2.50, 1.54, and 1.2 ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.44, 160.71, 149.45, 125.73, 99.35, 81.86, 66.95, 60.85, 60.27, 57.79, 53.35, 28.16, 14.36, 13.98.

lowered to about 4 with 6 M HCl. The mixture is cooled to about 0° C and filtered cold rinsing with cold water. The light brown solid is dried in a vacuum oven at 40° C for two days to afford 0.45 g (98%) of the title compound.

Physical characteristics are as follows:

^{1}H NMR (400 MHz, D_2O) δ 8.6, 7.68, 4.66, 4.00, 3.92, 3.38; ^{13}C NMR (100 MHz, D_2O) δ 174.00, 169.02, 155.00, 147.70, 129.53, 128.02, 127.41, 111.20, 64.17, 54.47, 51.75, 44.53.

PREPARATION 6. *N*-(4-Chlorobenzyl)-7-methyl-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.



7-Methyl-2-(4-morpholinomethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (1.09 g) from Preparation No. 5 and 1,1′-carbonyldiimidazole (0.86 g) are dissolved in dry *N,N*-dimethylformamide (9.8 ml) and heated to 65-70° C for 3.5 hr. To the reaction mixture is added 4-chlorobenzylamine (0.44 ml) and the mixture is heated for about 1.5 hr at 65-70° C. The reaction mixture is diluted with water (6.5 ml) and cooled to about 0° C. The crude product is filtered cold, washed with cold water, and is dried at about 45° C in a vacuum oven overnight to afford 1.29 g (85%) of the title compound.

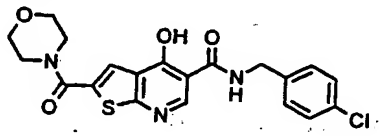
Physical characteristics are as follows:

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.61, 8.59, 7.41, 7.28, 4.61, 3.88, 3.72, 2.53.

Physical characteristics are as follows:

Mp 245-246 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60, 8.70, 7.54, 7.35, 7.29, 4.53, 3.96, 3.75, 3.59, 2.45; ^{13}C NMR ($CDCl_3$) δ 173.0, 165.0, 144.6, 137.9, 131.6, 129.3, 120.9, 115.7, 66.8, 57.6, 53.4, 43.1, 42.6; IR (drift) 2815, 1653, 1597, 1542, 1511, 1486, 1372, 1306, 1118, 1112, 1010, 865, 805, 798, 729 cm^{-1}; MS (ESI+) *m/z* 476 $(M+H)^+$. Anal. Found: C, 52.64; H, 4.66; N, 8.76; Br, 16.56; S, 6.65.

EXAMPLE 47. *N*-(4-Chlorobenzyl)-4-hydroxy-2-(4-morpholinylcarbonyl)-thieno[2,3-*b*]pyridine-5-carboxamide.

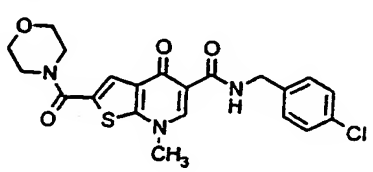


To a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-iodothieno[2,3-*b*]pyridine-5-carboxamide (2.00 g) from Example No. 2 in DMF (45 mL) are added triethylamine (1.25 mL), morpholine (15.7 mL), $Pd(OAc)_2$ (0.101 g), and dppp (0.186 g). The reaction mixture is degassed by bubbling N_2 through the solution for 15 minutes. Carbon monoxide is then bubbled through the solution, and the reaction mixture is heated to 70 °C and stirred for 18 h. The reaction mixture is allowed to cool to room temperature and water (25 mL) and 2 N HCl (75 mL) are added. The resulting green solid is filtered off and the filtrate is extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers are dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting orange oil is purified by column chromatography (CH_2Cl_2; CH_2Cl_2/methanol, 98/2). The resulting pale yellow solid is recrystallized from acetonitrile to yield 0.648 g (33%) of the title compound as an off-white solid.

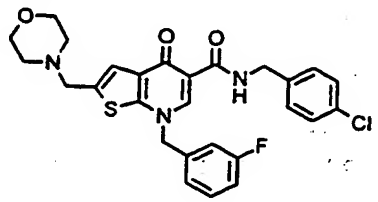
Physical characteristics are as follows:

Mp 217-219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72, 7.67, 7.31-7.25, 4.68, 3.86, 3.80; ^{13}C NMR ($CDCl_3$) δ 165.8, 162.3, 142.1, 136.3, 133.2, 131.7, 128.8, 128.7, 123.7, 66.7, 43.0; IR (drift) 2923, 2854, 2769, 2760, 1662, 1603, 1569, 1541, 1509, 1488, 1458, 1432, 1274, 1113, 791, cm^{-1}; MS (ESI-) *m/z* 430 $(M-H)^-$. Anal. Found: C, 55.47; H, 4.16; N, 9.76; Cl, 8.29; S, 7.50.

EXAMPLE 48. *N*-(4-Chlorobenzyl)-7-methyl-2-(4-morpholinylcarbonyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.



EXAMPLE 50. *N*-(4-Chlorobenzyl)-7-(3-fluorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.

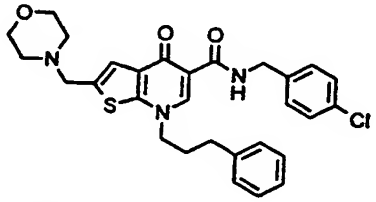


N-(4-Chlorobenzyl)-4-hydroxy-2-(4-morpholinylmethyl)thieno[2,3-*b*]pyridine-5-carboxamide (418 mg) from Example No. 41 and potassium carbonate (152 mg) are suspended in DMF (10 mL) and to the mixture is added 3-fluoro-benzylbromide (135 μL). The reaction mixture is allowed to stir at room temperature for 18 h. The resulting suspension is poured into water (10 mL), filtered, and washed with water (5 mL) followed by diethyl ether (5 mL). The resulting crude solid is purified by recrystallization from ethanol to afford 425 mg (81%) of the title compound as a white solid.

Physical characteristics are as follows:

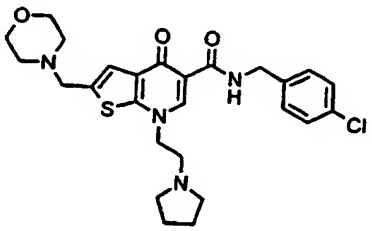
Mp 214-215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.55, 8.93, 7.48-7.12, 5.60, 4.55, 3.69, 3.55, 2.39; ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 164.2, 162.2 (d, J = 245 Hz), 149.6, 145.1, 138.4, 137.0, 131.4, 131.1, 129.2, 128.3, 123.6, 120.5, 115.5, 115.3, 114.8, 114.7, 114.5, 66.1, 58.2, 56.5, 52.9, 41.4; IR (drift) 1649, 1593, 1543, 1502, 1492, 1453, 1327, 1299, 1266, 1258, 1213, 1118, 1112, 808, 788 cm^{-1}; MS (ESI+) *m/z* 526 (100, $(M+H)^+$), 527 (30), 528 (40). Anal. Found ($C_{27}H_{25}ClFN_3O_3S$): C, 61.42; H, 4.81; N, 7.95; Cl, 6.70; S, 6.09.

EXAMPLE 51. *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(3-phenylpropyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.



N-(4-Chlorobenzyl)-4-hydroxy-2-(4-morpholinylmethyl)thieno[2,3-*b*]pyridine-5-carboxamide (418 mg) from Example No. 41 and potassium carbonate (152 mg) are suspended in DMF (10 mL) and to the mixture is added 1-bromo-3-phenylpropane (167 μL). The reaction mixture is allowed to stir at room temperature for 72 h. The reaction mixture is poured into water (25 mL) and extracted with EtOAc (2 x 25 mL). The organic layer is dried (Na_2SO_4) and concentrated. The resulting crude solid is purified by

EXAMPLE 53. *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-[2-(1-pyrrolidinyl)ethyl]-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.

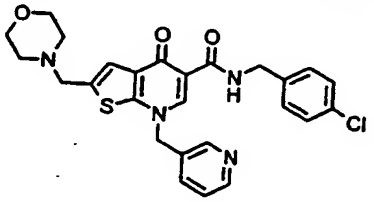


1,4-Diethylazodicarboxylate (205 μL) is added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(4-morpholinylmethyl)thieno[2,3-*b*]pyridine-5-carboxamide (418 mg) from Example No. 41, triphenylphospine (341 mg), and 1-(2-hydroxyethyl)pyrrolidine (292 μL) in THF (10 mL). The reaction mixture is stirred at room temperature for 20 h and then poured into 0.5 N aqueous NaOH solution (25 mL). The mixture is extracted with EtOAc (3 x 25 mL). The organic layer is dried (Na_2SO_4) and concentrated. The crude product is purified by column chromatography (CH_2Cl_2/methanol, 100/1; 50/1; 20/1; 10/1) followed by recrystallization from ethanol to afford 54 mg (11%) of the title compound as a white solid.

Physical characteristics are as follows:

Mp 178-180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.57, 8.69, 7.42-7.33, 4.53, 4.38, 3.75, 3.59, 2.89, 2.51-2.45, 1.69-1.62; IR (drift) 1651, 1592, 1559, 1532, 1502, 1457, 1327, 1296, 1143, 1119, 1110, 868, 811, 806, 800 cm1; MS (ESI+) *m/z* 515 (100, $(M+H)^+$), 516 (30), 517 (40). Anal. Found ($C_{26}H_{31}ClN_4O_3S$): C, 60.48; H, 6.04; N, 10.72; Cl, 6.99; S, 6.25.

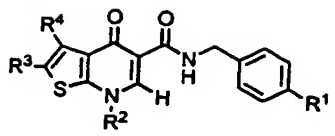
EXAMPLE 54. *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(3-pyridinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.



1,4-Diethylazodicarboxylate (205 μL) is added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(4-morpholinylmethyl)thieno[2,3-*b*]pyridine-5-carboxamide (418 mg) from Example No. 41, triphenylphospine (341 mg), and 3-pyridylmethanol (243 μL) in THF (10 mL). The reaction mixture is stirred at room temperature for 20 h and then the resulting suspension is filtered. The crude product is purified by recrystallization from ethanol to afford 63 mg (12%) of the title compound as a white solid.

What is claimed is:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof wherein,

R^1 is

(a) Cl,
(b) Br,
(c) CN,
(d) NO_2, or
(e) F;

R^2 is

(a) H,
(b) R^5,
(c) NR^7R^8,
(d) SO_2R^9, or
(e) OR^9;

R^3 is

(a) H,
(b) halo,
(c) aryl,
(d) $S(O)_mR^6$,
(e) $(C=O)R^6$,
(f) $(C=O)OR^9$,
(g) cyano,
(h) het, wherein said het is bound via a carbon atom,
(i) OR^{10},
(j) Ohet,
(k) NR^7R^8
(l) SR^{10},
(m) Shet,
(n) $NHCOR^{12}$,
(o) $NHSO_2R^{12}$, or

R^9 is

(a) aryl,
(b) het,
(c) C_{3-8}cycloalkyl, or
(d) C_{1-7}alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of $NR^{10}R^{10}$, R^{11}, SH, $CONR^{10}R^{10}$, and halo;

R^{10} is

(a) H, or
(b) C_{1-7}alkyl optionally substituted by OH;

R^{11} is

(a) OR^{10},
(b) Ohet,
(c) Oaryl,
(d) CO_2R^{10},
(e) het,
(f) aryl, or
(g) CN;

R^{12} is

(a) H,
(b) het,
(c) aryl,
(d) C_{3-8}cycloalkyl, or
(e) C_{1-7}alkyl optionally substituted by NR^7R^8 or R^{11};

R^{13} is

(a) $(P{=}O)(OR^{14})_2$,
(b) $CO(CH_2)_nCON(CH_3)\text{-}(CH_2)_nSO_3^-M^+$,
(c) an amino acid,
(d) C(=O)aryl, or
(e) $C(=O)C_{1-7}$alkyl optionally substituted by NR^7R^8, aryl, het, CO_2H, or $O(CH_2)_nCO_2R^{14}$);

R^{14} is

(a) H, or
(b) C_{1-7}alkyl;

each i is independently 2, 3, or 4;
each n is independently 1, 2, 3, 4 or 5;
each m is independently 0, 1, or 2; and
M is sodium, potassium, or lithium;

10. The compound of claim 1 wherein R^2 is methyl, ethyl, isopropyl, 2-hydroxyethyl, 2-(diethylamino)ethyl, or 2-(dimethylamino)ethyl.

11. The compound of claim 1 wherein R^3 is H, halo, $S(O)_mR^e$, $(C=O)R^e$, $(C=O)OR^9$, cyano, or C_{1-7}alkyl, which may be partially unsaturated and optionally substituted by one or more substituents of the group R^{11}, OR^{13}, SR^{10}, SR^{13}, NR^7R^8, halo, $(C=O)C_{1-7}$alkyl, and SO_mR^9.

12. The compound of claim 1 wherein R^3 is C_{1-7}alkyl which may be partially unsaturated and optionally substituted by one or more substituents of the group R^{11}, OR^{13}, SR^{10}, SR^{13}, NR^7R^8, halo, $(C=O)C_{1-7}$alkyl, and SO_mR^9.

13. The compound of claim 1 wherein R^3 is C_{1-7}alkyl which may be partially unsaturated and is substituted by one or more substituents of the group R^{11}, OR^{13}, SR^{10}, SR^{13}, NR^7R^8, halo, $(C=O)C_{1-7}$alkyl, and SO_mR^9;

14. The compound of claim 1 wherein R^3 is C_{1-7}alkyl which may be partially unsaturated and is substituted by one or more substituents of the group OR^{10}, het and NR^7R^8.

15. The compound of claim 1 wherein R^3 is bromo, iodo, 3-hydroxy-1-propynyl, 3-methoxy-1-propynyl, 4-hydroxy-1-butynyl, 3-hydroxypropyl, cyano, 4,4-di(methoxy-carbonyl)-1-butynyl, 4-hydroxybutyl, 3-(3-carboxypropanoyloxy)-1-propynyl, 3-(morpholinoacetoxy)-1-propynyl, 3-(2-amino-3-methylbutanoyloxy)-1-propynyl, or thiomorpholinomethyl, N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-N-(methyl)aminomethyl, morpholinocarbonyl, 3-[3-(morpholinomethyl)benzoyloxy]-1-propynyl.

16. The compound of claim 1 wherein R^3 is iodo, 3-hydroxy-1-propynyl, 4-hydroxy-1-butynyl, 3-hydroxypropyl, morpholimomethyl, N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-N-(methyl)aminomethyl or 4-hydroxybutyl.

17. The compound of claim 1 wherein R^3 is 3-hydroxy-1-propynyl, morpholimomethyl, N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-N-(methyl)aminomethyl or 3-hydroxypropyl.

(18) *N*-(4-Chlorobenzyl)-7-[2-(diethylamino)ethyl]-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(19) 2-[5-{[(4-Chlorobenzyl)amino]carbonyl}-2-(3-hydroxy-1-propynyl)-4-oxothieno[2,3-*b*]pyridin-7(4H)-yl]acetic acid;

(20) *N*-(4-Chlorobenzyl)-7-ethyl-2-(4-hydroxybutyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(21) *N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(22) *N*-(4-Chlorobenzyl)-7-[2-(diethylamino)ethyl]-2-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(23) *N*-(4-Chlorobenzyl)-2-iodo-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide;

(24) *N*-(4-Chlorobenzyl)-2-(3-hydroxy-1-propynyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(25) *N*-(4-Chlorobenzyl)-2-(3-hydroxypropyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(26) *N*-(4-Chlorobenzyl)-2-iodo-7-isopropyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide;

(27) *N*-(4-Chlorobenzyl)-2-(3-hydroxy-1-propynyl)-7-isopropyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(28) *N*-(4-Chlorobenzyl)-2-(3-hydroxypropyl)-7-isopropyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(29) 4-{[3-(5-{[(4-Chlorobenzyl)amino]carbonyl}-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-2-propynyl]oxy}-4-oxobutanoic acid;

(30) 3-(5-{[(4-Chlorobenzyl)amino]carbonyl}-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-2-propynyl 2-(4-morpholinyl)acetate;

(31) 3-(5-{[(4-Chlorobenzyl)amino]carbonyl}-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-2-propynyl 2-amino-3-methylbutanoate;

(32) 3-(5-{[(4-Chlorobenzyl)amino]carbonyl}-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-2-propynyl 3-(4-morpholinylmethyl)benzoate;

(33) Methyl-5-{[4-chlorobenzyl)amino]carbonyl}-4-hydroxythienol[2,3-b]pyridine-2-carboxylate;

(50) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(3-phenylpropyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(51) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(tetrahydro-2-furanylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(52) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-[2-(1-pyrrolidinyl)ethyl]-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(53) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(3-pyridinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(54) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(4-pyridinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide; or

a pharmaceutically acceptable salt thereof.

19. The compound of claim 1 which is:

(1) *N*-(4-Chlorobenzyl)-7-ethyl-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide;

(2) *N*-(4-Chlorobenzyl)-7-ethyl-2-(4-hydroxy-1-butynyl)-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide;

(3) *N*-(4-Chlorobenzyl)-7-ethyl-2-(3-hydroxypropyl)-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide;

(4) *N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(5) *N*-(4-Chlorobenzyl)-7-[2-(diethylamino)ethyl]-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(6) *N*-(4-Chlorobenzyl)-7-ethyl-2-(4-hydroxybutyl)-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide;

(7) *N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(8) *N*-(4-Chlorobenzyl)-7-[2-(diethylamino)ethyl]-2-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(9) *N*-(4-Chlorobenzyl)-2-iodo-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide;

(10) *N*-(4-Chlorobenzyl)-2-(3-hydroxy-1-propynyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(27) *N*-(4-bromobenzyl)-7-methyl-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(28) 7-Benzyl-*N*-(4-chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(29) *N*-(4-Chlorobenzyl)-7-(3-fluorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(30) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(3-phenylpropyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(31) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(tetrahydro-2-furanylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(32) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-[2-(1-pyrrolidinyl)ethyl]-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(33) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(3-pyridinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(34) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(4-pyridinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide; or

a pharmaceutically acceptable salt thereof.

20. The compound of claim 1 which is:

(1) *N*-(4-Chlorobenzyl)-7-ethyl-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(2) *N*-(4-Chlorobenzyl)-7-ethyl-2-(4-hydroxy-1-butynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(3) *N*-(4-Chlorobenzyl)-7-ethyl-2-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(4) *N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(5) *N*-(4-Chlorobenzyl)-7-[2-(diethylamino)ethyl]-2-(3-hydroxy-1-propynyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(6) *N*-(4-Chlorobenzyl)-7-ethyl-2-(4-hydroxybutyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(7) *N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(24) 7-Benzyl-*N*-(4-chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(25) *N*-(4-Chlorobenzyl)-7-(3-fluorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(26) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(tetrahydro-2-furanylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(27) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-[2-(1-pyrrolidinyl)ethyl]-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(28) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(3-pyridinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(29) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-(4-pyridinylmethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide; or

a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 which is:

(1) *N*-(4-Chlorobenzyl)-7-[2-(diethylamino)ethyl]-2-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(2) *N*-(4-Chlorobenzyl)-2-(3-hydroxy-1-propynyl)-7-methyl-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide;

(3) *N*-(4-Chlorobenzyl)-2-(3-hydroxypropyl)-7-methyl-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide;

(4) *N*-(4-chlorobenzyl)-7-methyl-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(5) *N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-(4-hydroxyphenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(6) *N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(7) *N*-(4-Chlorobenzyl)-7-ethyl-2-(4-morpholinylmethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide;

(8) *N*-(4-Chlorobenzyl)-2-(4-morpholinylmethyl)-4-oxo-7-propyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide; or

a pharmaceutically acceptable salt thereof.

R^{34} is C_{1-7}alkyl optionally substituted R^{33};

R^{35} is C_{1-7}alkyl, aryl or het;

R^{36} is CO_2H or CO_2C_{1-7}alkyl

each n is independently 1, 2, 3, 4, or 5;

each m is independently 0, 1, or 2;

M is a pharmaceutically acceptable cation (e.g. sodium, potassium, or lithium);

wherein any aryl, or het is optionally substituted with one or more substituents (e.g. 1, 2, 3, 4, or 5) independently selected from the group consisting of halo, cyano, trifluoromethyl, trifluoromethoxy, hydroxy, carboxy, OR^{27}, phenyl, phenoxy, (C_{1-7}alkoxy)carbonyl, SR^{31}, and C_{1-7} alkyl optionally substituted with one or more substituents independently selected from the group consisting of cyano, aryl, mercapto, het, R^{36}, OR^{27}, SR^{27}, and SR^{31}; wherein phenyl or phenoxy is optionally substituted with one or more substituents independently selected from cyano, halo, trifluoromethyl, trifluoromethoxy, carboxy, het, OR^{31}, and R^{27}.

24. A pharmaceutical composition comprising a compound of any one of claims 1 to 23 and a pharmaceutically acceptable excipient.

25. A compound of any one of claims 1 to 23 for use in medical treatment.

26. The compound of claim 25 wherein the treatment is the treatment or prevention of a herpesviral infection.

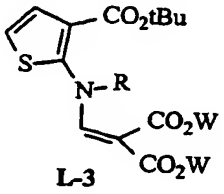
27. The compound of claim 26 wherein the herpesviral infection is herpes simplex virus type 1, 2, 6, 7, or 8, varicella zoster virus, human cytomegalovirus, or Epstein-Barr virus.

28. The compound of claim 26 wherein the herpesviral infection is herpes simplex virus type 1, herpes simplex virus type 2, varicella zoster virus, human cytomegalovirus, Epstein-Barr virus, human herpes viruses 7 or human herpes viruses 8.

29. The compound of claim 26 wherein the herpesviral infection is human cytomegalovirus.

30. The use of a compound of any one of claims 1 to 23 to prepare a medicament for treating or preventing a herpesviral infection in a mammal.

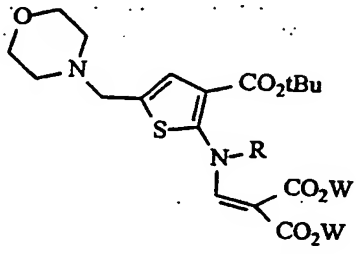
alkylating the compound of formula L-2 to provide a corresponding compound of formula L-3:



L-3

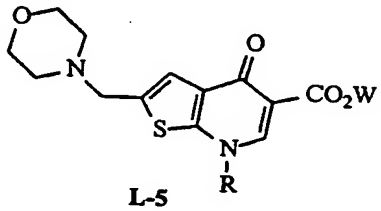
wherein R is C_{1-4}alkyl;

reacting the compound of formula L-3 with a 4-methylenemorpholinium salt to provide a compound of formula L-4:



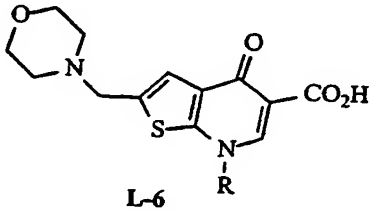
L-4

cyclizing the compound of formula L-4 to provide a bicyclic ester of formula L-5:



L-5

hydrolyzing the ester of formula L-5 to provide a carboxylic acid of formula L-6:



L-6

and

37. The compound of claim 34, 35, or 36 wherein R is methyl and W is ethyl.

38. The compound:

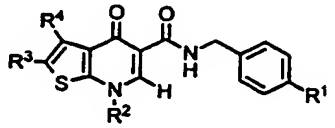
(1) *N*-(3-*tert*-butoxycarbonyl-thien-2-yl)methylaminomethylenemalonic acid diethyl ester;

(2) *N*-(3-*tert*-butoxycarbonyl-5 morpholinomethyl-thien-2-yl)methylaminomethylenemalonic acid diethyl ester;

(3) ethyl 7-methyl-2-(4-morpholinomethyl)-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate; or

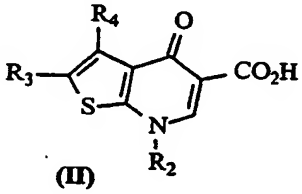
(4) 7-methyl-2-(4-morpholinomethyl)-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid.

39. A method for preparing a compound of formula I:



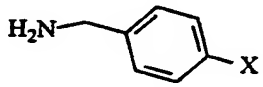
I

wherein R^1-R^4 have the values described in claim 1, comprising reacting a corresponding carboxylic acid of formula (II):



(II)

with a benzylamine of the formula:



wherein X is Cl, Br, CN, NO_2, or F, to provide the compound of formula (I).

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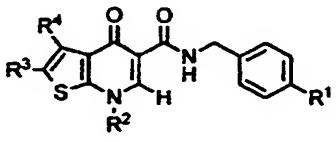
(54) Title: 4-OXO-4,7-DIHYDRO-THIENO[2,3-b]PYRIDINE-5-CARBOXAMIDES AS ANTIVIRAL AGENTS



I (I)

(57) Abstract: The invention provides a compound of formula (I), wherein R^1, R^2, R^3, and R^4 have any of the values defined in the specification, or a pharmaceutically acceptable salt thereof, as well as processes and intermediates useful for preparing such compounds or salts, and methods of preventing or treating a herpesvirus infection using such compounds or salts.

WO 00/53610 A3

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 00/05937

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 817 819 A (KATO KOICHI ET AL) 6 October 1998 (1998-10-06) cited in the application column 22; figure 1	34
A	column 22 -column 24 column 50; table 2 column 71; table 13	1,23-25, 30,31, 33,35

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 00/05937

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D513/04 C07D333/38 A61K31/435 A61P31/22 A61P31/20
//(C07D513/04,333:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 959 363 A (WENTLAND MARK P) 25 September 1990 (1990-09-25) abstract; claims	1,23-25, 30,31
A	WO 98 11073 A (TUCKER JOHN A ;UPJOHN CO (US); ROMERO ARTHUR G (US); ROMINES KAREN) 19 March 1998 (1998-03-19) abstract; claims 1,5,7,8	1,23-25, 30,31
A	EP 0 443 568 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 28 August 1991 (1991-08-28) cited in the application abstract; claims page 28 -page 29; table 8A page 25; table 6A	1,23-25, 30,31

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2000	07/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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INTERNATIONAL SEARCH REPORT

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International Application No
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